Control Your Cell Fate:

How the Mammary Microenvironment Redirects the Fate of Stem Cells

No cancer cell is an island; carcinogenesis does not occur in isolation. Rather, the cellular interactions and cross talk that take place within its microscopic ecosystem help to drive the uncontrolled growth that results in tumor formation. The development and progression of every cell's fate—normal or cancerous—is shaped by the chemical signals released by the multitudes of other cells that lie in its neighborhood: its microenvironment. It follows, therefore, that modulation of this microenvironment can alter cellular differentiation.

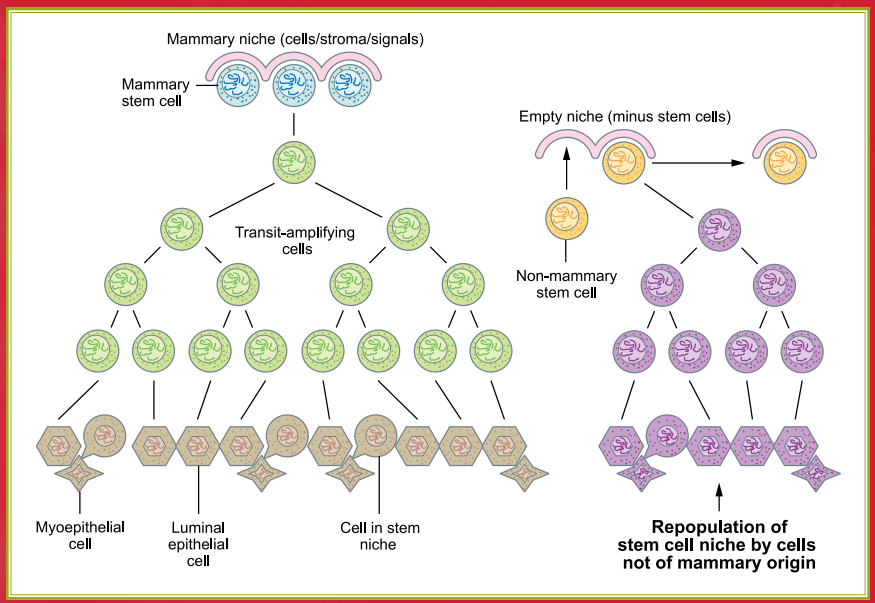
Several studies have demonstrated the dominance of the cellular niche over stem cells during normal development, showing that cell fate can be redirected across lineage boundaries in various models. In the September 2008 issue of *The Proceedings of the National Academy of Sciences*, Gilbert Smith, Ph.D., Senior Investigator and Head of the Mammary Stem Cell Biology Section at CCR, and his colleagues further illuminate how tissue-specific signals of differentiated somatic cells alter adult stem cell fates. Specifically, they show that neural stem cells (NSCs) can be reprogrammed into mammary epithelial-cell lineages simply by mixing mammary epithelial cells (MECs) in the mammary fat pad.

In a study published a year previously, Dr. Smith and colleagues demonstrated that cells isolated from a mature testis, when mixed with normal MECs in the context of a mammary fat pad, cooperated with these cells and contributed progeny to normal mammary epithelial outgrowth and normal mammary function. But because the testicular cells were comprised of about 10 percent germinal stem cells and 20 percent Sertoli cells, with the remainder of the cells from spermatozoa lineage, the researchers were unable to distinguish which cells were being reprogrammed. To overcome this limitation, the researchers turned to isolated NSCs that could be maintained *in vitro*.

The researchers found that the purified cell population could be reprogrammed successfully using the same protocols as in their previous study. The bona fide NSCs could be reprogrammed into multipotent MECs with the capacity to produce progeny that differentiate into secretory or myoepithelial cells. This indicates that cellular signals from the mammary microenvironment were capable of redirecting the NSCs to form mammary cells. The team is currently engaged in studies to understand how these microenvironmental signals direct mammary cell growth and how those signals might be challenged to control the overproduction of mammary epithelial cells that results in breast cancer.

"Recently, we have extended our studies to include cancer cells; they have been shown by earlier investigators to be responsive to normal developmental environments," said Dr. Smith. "A way to think about cancer is as a developing tissue where the microenvironment of the tumor promotes tumor expansion, development, and growth... So if cancer cells can respond normally to a non-tumor microenvironment, it might be possible to determine what factors might control the growth and expansion of cancer *in situ*." This work points to a promising new direction for therapeutic research. Modulation of the cellular microenvironment to redirect cellular differentiation pathways may one day be used to "normalize" malignant cancer cells.

To learn more about Dr. Smith's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?Name=gsmith.



(Image: J. Kelly)

Cellular signals from the mammary microenvironment redirect the fates of non-mammary stem cells.